

THE BRITISH JOURNAL OF DERMATOLOGY

DECEMBER 1959

TINEA PEDIS IN A GROUP OF SCHOOLCHILDREN.

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DURING the year 1957, a group of 387 schoolchildren, pupils of an intermediate school in Dunedin, was investigated for the presence of tinea pedis. Intermediate schools in New Zealand cater for children in the last two grades of primary education. Most children enter such a school at 11 or 12 years of age, and, after two years' attendance, pass on to a secondary school. A few, however, do not seek a secondary education, and these remain at the intermediate school, until they reach the school-leaving age of 15 years.

The ages of the children included in this study ranged from 11 to 14 years, but the age groups were not evenly distributed and more than half the subjects investigated were in their thirteenth year. The school was notable for its prowess in swimming, its teams having been successful in a number of contests, and we selected its pupils for study, primarily to determine whether the incidence of tinea pedis was affected by participation in this sport. For this reason, special attention was paid to the swimming habits of each child, but the effects of certain other environmental factors were also investigated.

MATERIAL AND METHODS.

The name, sex and age of each child was recorded on a punch card and information on the swimming habits, the type of shoes worn in school and the military service of the father was obtained. The children were asked whether they suffered from any interdigital discomfort, but their answers on this point appeared to be too indecisive to be reliable, so the incidence of subjective symptoms has been omitted from this study.

The child's feet were then inspected and their general structure and hygienic condition recorded. Personal hygiene was recorded as good or poor, classification being governed to some extent by smell. If the feet smelt strongly, the dirt was ingrained, or the toenails long and dirty, the hygiene was recorded as "poor". In

view of the fact that the children received no warning of the foot examination, the standard of foot hygiene was remarkably good.

The hydrogen ion concentration of the fourth interdigital space on each foot was tested by using pH papers (Johnsons of Hendon Ltd.) which were left in the interspace while the history was being taken. Then the interspaces were inspected and the presence of any scaling, maceration or fissures was recorded. The presence of verrucae, chilblains and other clinical abnormalities of the feet was also reported. In a limited number of subjects, the first and fourth interdigital spaces of one foot were sampled with a swab moistened with sterile nutrient broth. These swabs were used to inoculate human blood agar plates which were incubated overnight at 37° C. A slide coagulase test was carried out on all staphylococci isolated, and positive results were confirmed by a tube test. The presence of diphtheroids, streptococci, coliforms and other organisms was recorded, but complete identification was omitted.

To determine whether the presence of pathogenic staphylococci in the interspaces was associated with nasal carriage, nasal swabs were taken from a proportion of these subjects and inoculated on to blood agar plates which were treated in the same way as the cultures made from the feet. The interdigital spaces of all the children were then cleaned with methylated spirits and ether and were sampled for the presence of a pathogenic fungus. With a sterile blunt scalpel, scrapings were taken from the fourth interspace of each foot, except in a few cases where scaling or maceration was more obvious elsewhere. At least four cultures were made from each subject, using Sabouraud's glucose agar, malt tellurite agar and honey agar. Further scrapings from both feet were mounted in 10% KOH and later examined microscopically. In a small series of subjects, the fifth toenail from each foot was clipped and the fragments examined microscopically after boiling in 10% KOH. Fungus cultures were incubated at 27° C. and inspected after 7, 10, 14 and 21 days after which negative tubes were discarded. Yeast-like isolates were subcultured on to Difco chlamydospore agar, incubated for 48 or 72 hours in a candle jar at room temperature and then examined for the presence of growth, mycelium and chlamydospores. Isolates which grew and produced chlamydospores were identified as *Candida albicans*. The rest were recorded as non-pathogenic yeasts and a small number of strains were sent to Dr. M. E. di Menna, who kindly consented to identify them.

The macroscopic and microscopic appearances of dermatophytes were recorded, and all isolates of Trichophyta were subcultured on cornmeal glucose agar, a medium recommended by Haley and Stonerod (1954) for increasing pigment production and facilitating the differentiation of *T. rubrum* from *T. mentagrophytes*.

RESULTS.

The results listed below were obtained by the investigation of 184 boys and 203 girls. Table I summarises the results obtained from the history and clinical examination. The most striking feature of the clinical examination was the high incidence of scaling and maceration in the interdigital spaces of these young children. In only 30% was the skin of the interspaces smooth and unbroken. The rest showed at least some scaling, while in 26% the skin was thick and macerated and in 9% fissures were present. Even in those children with the most extensive lesions, however, subjective symptoms appeared to be minimal.

The children classes as "frequent swimmers" were those who visited the swimming baths regularly and at least once a week. "Occasional swimmers"

TABLE I.—*Clinical Findings in Groups of School Children.*

Information	11 yrs.	12 yrs.	13 yrs.	14 yrs.	Total	
Number examined	66	220	78	23	387	
Frequent swimmer	45.4	39.0	43.6	21.7	40.0	} %
Occasional swimmer	31.8	30.5	33.3	34.8	31.2	
Non-swimmer	22.8	30.5	23.2	43.5	28.8	
Father in Armed Forces in World War II	57.6	56.9	51.3	47.8	55.3	
Poor hygiene	15.1	22.3	19.2	17.4	20.2	
pH of 4th interspace examined in	61	205	63	14	343	
pH 6.4 or less*	31.1	31.2	20.6	0.0	28.0	} %
„ 6.5-7.1	32.8	31.2	25.4	42.8	30.9	
„ 7.2-7.9	21.3	21.0	22.1	0.0	20.4	
„ 8 or more	14.8	16.6	31.9	57.2	20.7	
Chilblains†	6.1	5.9	2.6	4.3	5.2	
Warts	4.5	1.4	3.8	8.7	2.9	} %
Interdigital skin normal	30.3	35.0	24.4	13.0	30.7	
Interdigital space scaling	69.7	65.0	75.6	87.0	69.3	
Macerated skin present	27.3	25.9	33.3	43.5	26.1	
Fissures present	12.2	6.8	8.9	21.7	9.0	
Pathogenic fungus present	4.5	5.4	8.9	4.3	5.9	

* Where the reaction differed in the two interspaces, the more alkaline reading was recorded.

† All but one case occurred in girls.

were those who bathed in the sea, or the swimming baths only in the summer. The incidence of 28.8% of “non-swimmers” appears to be rather high in a school situated in a seaside town, but owing to its geographical position, the sea round Dunedin remains incredibly cold, even on the hottest day.

The feet appeared to be badly cared for in 20% of the children. Many more had superficially dirty feet, but as most of the children were wearing dark socks and gymnastic shoes, this was not surprising. Those children whose interspaces were easily cleaned in preparation for the mycological sampling were not regarded as having poor personal hygiene.

It seemed possible that the record of poor hygiene might be due to the smell noticed by the investigator, which could result from the wearing of gymnastic shoes, the presence of maceration, or the presence of a pathogenic fungus or some other micro-organism. The results obtained from the 78 subjects recorded as having “poor hygiene” were therefore analysed and compared with those obtained from the rest. It was found that the swimming habits, type of shoe and kinds of micro-organisms isolated showed the same distribution in the two groups. It seems therefore that although the assessment of personal hygiene was subjective it was reasonably accurate.

The results obtained from the attempts to measure the reaction of the interspaces were not very accurate, but they seem to indicate that Marchionini's “acid mantle” of the skin breaks down in the interdigital spaces of the foot. In 41% an alkaline reaction was recorded. This appeared to be closely associated with the presence of dead and macerated skin. In 96 children, the interspaces of both feet had a pH of 6.4 or less and of these 57.3% had normal interspaces and only 9.4% showed any maceration. In the 69 children in whom

a pH of 8.0 or more was recorded, only 5.8% had apparently normal interspaces, while 55% showed considerable maceration. It seems possible that the alkaline environment in the macerated space is the result of microbial action, but no significant qualitative difference in the aerobic flora of the acid or alkaline interspace could be detected.

Chilblains were present in 19 girls but only 1 boy. Warts, mainly plantar, were present in 2.9% and were equally distributed between the two sexes. A number of other clinical abnormalities was observed. Overlapping and deformed toes were found in 9 children and a further 5 had hammer toes. Corns were found on the feet of 4 subjects, a rather disturbing finding in this young age group. In one child the fifth toenails were congenitally absent, while in another onychogryphosis was present. Impetigo occurred twice, boils, eczema and ichthyosis once each.

Table II shows the micro-organisms isolated from the normal and abnormal interdigital spaces. In spite of the high incidence of clinical abnormality, the presence of a pathogenic fungus could be demonstrated in only 23 subjects (5.9%), although twice the number of tubes were inoculated than in a previous investigation of university students which yielded an incidence of more than 20% (Marples and Bailey, 1957). The incidence was slightly lower in girls than in boys, but the difference was not statistically significant. A pathogenic fungus was isolated from three subjects with apparently normal skin, while the rest showed varying degrees of scaling and maceration.

TABLE II.—*Micro-Organisms Isolated from the Interdigital Spaces.*

	Interspace clinically normal	Interspace clinically abnormal	Total
Number examined mycologically . . .	119	268	387
Pathogenic fungus demonstrated . . .	3 (2.5%)	20 (7.5%)	23 (5.9%)
Non-pathogenic yeast present . . .	23 (19.3%)	66 (24.6%)	89 (23.0%)
Number examined bacteriologically . . .	72	129	201
Coagulase positive staphylococcus present . . .	1 (1.4%)	4 (3.1%)	5 (2.5%)
Diphtheroid present . . .	28 (38.9%)	65 (50.4%)	93 (46.5%)

Coagulase positive staphylococci were recovered from only 2.5% of the interdigital spaces. Their absence may account for the lack of definite subjective symptoms, since in a previous study (Marples and Bailey, 1957) it was found that pathogenic staphylococci could be isolated from the interspaces of 64.7% of those who complained of itching and burning, but only 9.4% of those with an asymptomatic abnormal interspace. Coagulase negative staphylococci were isolated from almost all subjects and diphtheroids were also commonly encountered.

Non-pathogenic yeasts were isolated from 23.0% of the interspaces sampled. Most of the isolates failed to grow on chlamydospore agar. A small number of

these strains was examined by Dr. M. E. di Menna, who identified the majority as *Debaryomyces klockeri*. Table III lists the mycological findings. Fungal hyphae were found in direct microscopic examination of scrapings from 15 subjects. In 45 children, nail clippings were taken in addition to interdigital skin. In only one preparation were fungal hyphae detected and these were also present in the skin scrapings taken from the same child, so that examination of nail clippings did not assist in the detection of a pathogenic fungus.

TABLE III.—*Mycological Findings.*

Pathogenic fungus demonstrated	23
Fungal elements seen in direct examination	15
Pathogen isolated in culture	16
<i>Trichophyton mentagrophytes</i>	12
<i>Trichophyton</i> spp.	2
<i>Epidermophyton floccosum</i>	1
<i>Candida albicans</i>	1

Only 16 isolates of a pathogenic fungus were obtained and two of these recorded as *Trichophyton* spp. were badly contaminated and could not be identified further. Twelve strains of *Trichophyton mentagrophytes* were isolated but no strains of *T. rubrum* were recovered although a careful search for the species was made. A few of the isolates of *T. mentagrophytes* produced some red pigment especially on malt tellurite medium, but failed to do so on corn-meal glucose agar, nor were the microscopic findings those of *T. rubrum*. It seems clear that this pathogen is still comparatively rare in Dunedin, although it is being increasingly isolated from material sent to our laboratory from the northern parts of New Zealand. One strain each of *Epidermophyton floccosum* and *Candida albicans* was recovered. The presence of a pathogenic fungus in the child's interdigital space did not appear to be associated with the swimming habits, type of footwear, personal hygiene, pH of the interspace, or with the military service of the father.

Nasal swabs were taken from 90 subjects and coagulase positive staphylococci were isolated from 13 (14·4%), but only three (3·3%) of these subjects also carried pathogenic staphylococci in the interdigital space, while two foot carriers had only coagulase negative strains in the nose.

DISCUSSION.

The most obvious conclusion to be drawn from the results of the present study and their comparison with those obtained by other workers is that the presence of a pathogenic fungus is not the only aetiological factor in the development of an abnormal interdigital space. Two lines of evidence support this conclusion. The first is the discrepancy between the incidence of interdigital damage and the proven presence of a fungal pathogen. The findings in recent

surveys are surprisingly uniform. Ajello *et al.* (1945) observed fungal elements in scrapings in only 17.7% of 871 young men entering military service, although clinical evidence of infection was found in 59.9%. Gentles and Holmes (1957), in their impressive study of foot ringworm in coal miners, report an incidence of 21% of proven dermatophyte infection, although 90% of the 2101 subjects they examined had scaling or macerated interdigital skin. In two studies on university students carried out in Dunedin (Marples and di Menna, 1949; Marples and Bailey, 1957), the incidence of dermatophyte infection was found to be 17.8 (in males) and 20.6% respectively, although maceration and scaling of the fourth interdigital space was found in 65 and 75% of 568 and 175 subjects. The discrepancy appears to be present in younger age groups. English and Gibson (1957) have published a preliminary report on interdigital infection in children. They found that 37% of 931 boys aged 11 and 12 years and 42.2% of 896 aged 13 and 14 years showed some interdigital abnormality. They only examined material from the damaged interspaces and obtained evidence of mycotic infection in 17.7% and 15.8% of the respective age groups, the overall incidence being 6.7% in both. If they had taken scrapings from apparently normal spaces, this figure might have been slightly higher. They reported that the incidence in different schools varied from 3.2 to 8.9%. The results obtained in Dunedin of 69% clinical abnormality but only 5.9% fungal infection in a similar age group are in close agreement with these British findings. Scheffler (1958), in Germany, reported rather different findings. He examined the feet of 2,622 schoolchildren and found that only 19% of the girls and 29% of the boys had clinical evidence of fungous infection. However, laboratory confirmation was obtained in 43% of the girls and 34% of the boys. This gives an overall figure of 9% proven infection, which is in agreement with British and New Zealand results.

The second piece of evidence in favour of the view that fungal infection is not the only cause of interdigital scaling and maceration is the constant recovery of a pathogenic fungus from a small proportion of apparently normal interspaces. Ajello and his colleagues (1945) observed fungal elements in 1.7% of 349 subjects without clinical infection, while Gentles and Holmes (1957) isolated a dermatophyte from 2.5% of 201 clinically normal subjects. In Dunedin, the recovery rate in university students has been 3.3 and 8.9% while 2.5% of 119 schoolchildren with apparently normal interdigital spaces were shown to be carrying a dermatophyte.

A number of explanations of the presence of a pathogenic fungus in undamaged interdigital skin can be postulated. One is that the subject is incubating an infection, which has not yet produced clinical signs. Follow-up examination of individuals in this category might clarify this problem, but they have not been feasible in Dunedin. Another possibility is that the fungus is living in the toenails and that while the interdigital skin is normal, the nail is not. In the

present investigation, an attempt was made to record abnormalities of the toe-nails, but the distinction between normal and abnormal nails was found too difficult to be reliable. The series of nail clippings examined microscopically is too small to be conclusive but it is of interest that fungal hyphae were readily demonstrated in the interdigital scrapings of the only child whose nail clippings were proved to be infected. A third possibility which cannot be ignored is that a pathogenic fungus can live in an interdigital space without causing any visible damage.

Information on the bacterial flora of the interdigital spaces of the foot is scanty. Wallace and Moorman (1943) carried out a bacteriological and mycological examination of 60 high school students, 8 of whom had active dermatophytosis. They reported that isolates of *Staphylococcus aureus* and *Staphylococcus albus* predominated, but they did not distinguish between pathogenic and non-pathogenic strains. In the Dunedin school children, coagulase negative staphylococci were isolated from over 90% of the interspaces sampled, but coagulase positive strains from only 2.5%. This low level of infection, together with the lack of decisive subjective symptoms in the group appears to support the theory previously offered (Marples and Bailey, 1957) that the presence of a pathogenic staphylococcus in the interdigital space is associated with the development of subjective symptoms even in the absence of observed inflammatory response.

Meenan (1953) postulated that the development of scaling and maceration in the interdigital spaces might be entirely due to hyperidrosis and that "fungi, although potentially pathogenic, are living at peace with their host in his warm, moist interdigital skin." The present study supports this hypothesis and it seems possible that in the development of clinical tinea pedis, the following sequence of events occurs. The interdigital skin becomes macerated and is desquamated in large fragments in early adolescence as a result of hyperidrosis, probably accentuated by the horrible woollen socks or stockings which most school children are forced to wear. Pathogenic fungi find this environment suitable, colonise the area and stimulate a mild host response, part of which may be allergic and the lesion is extended. Pathogenic staphylococci readily colonise damaged skin as Stuart-Harris (1948), Pillsbury and Kligman (1954) and other authorities have shown. These bacterial pathogens become established in the lesion already infected by a pathogenic fungus and the association of the mycotic and bacterial invaders increases the host response to a level of conscious awareness. If this interpretation of the sequence of events is correct, it provides strong support for Meenan's (1953) view that cases of fissuring, maceration or scaling between the toes should be thoroughly investigated and that vigorous therapy to eliminate a non-existent fungus should be avoided.

The absence of any demonstrable connection between environmental factors and the incidence of foot ringworm in the present study was disappointing.

Gentles and Holmes (1957) have demonstrated that, among the miners studied, the regular use of communal baths was the most important factor in the development of interdigital mycotic infection. No such association could be demonstrated in Dunedin school children. English (1957) reported the results of an interesting study of the spread of *Trichophyton rubrum* infection in families, while Ingram and La Touche (1957) recorded familial spread of other interdigital pathogens. Although many New Zealand servicemen suffered from foot ringworm during and since World War II, no significant association between infection of the child and military service by the father could be demonstrated in the present study. It seems probable that the incidence of infection in the age group studied was too low to permit satisfactory assessment of the effect of environmental factors. A further study carried out on an older age group might increase our understanding of the ecology of foot ringworm.

SUMMARY.

1. The incidence of tinea pedis in 387 school children between the ages of 11 and 15 years was investigated.
2. Scaling and maceration of one or more interdigital spaces of the foot was found in 69.3%.
3. The presence of a pathogenic fungus was demonstrated in 2.5% of those with apparently normal skin, in 7.5% of abnormal interspaces, the overall incidence being 5.9%.
4. The incidence of mycotic infection did not differ significantly between the sexes, or in the different age groups.
5. *Trichophyton mentagrophytes* predominated among the fungal isolates. No strains of *T. rubrum* were recovered. Non-pathogenic yeasts were isolated from 23% of the interdigital spaces.
6. The presence of a pathogenic fungus could not be associated with the swimming habits of the child, the type of shoes worn, the reaction of the interspace, the level of personal hygiene, or the military service of the father.
7. A coagulase positive staphylococcus was isolated from the interdigital spaces of 2.5% of 201 children. Nasal swabs were taken from 90 children and 14.4% yielded pathogenic staphylococci. Pathogenic staphylococci were isolated from both nose and interdigital space of only 3.3%.
8. The results of the investigation are compared with those obtained elsewhere and the conclusion is reached that abnormality of interdigital skin is not necessarily the result of dermatophyte infection. It is suggested that scaling and maceration appear first, probably as the result of hyperhidrosis and that the damaged skin is colonised by a pathogenic fungus. Secondary colonisation by a pathogenic staphylococcus may be responsible for the development or exacerbation of subjective symptoms.

Our thanks are due to the staff and students of the Dunedin North Intermediate School for facilitating this investigation; to Dr. M. E. di Menna, Soil Bureau Experimental Station, Taita, for the identification of non-pathogenic yeasts; to Mr. G. Spears, Department of Preventive Medicine for statistical analysis of the figures; to Professor J. A. R. Miles, and the staff of the Department of Microbiology for laboratory facilities and especially to Miss M. Watt and Mrs. D. Craven for their continuous assistance in the clinical and laboratory investigations.

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CHRONIC PARONYCHIA. A MYCOLOGICAL AND BACTERIOLOGICAL STUDY.

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MUCH has been written about chronic paronychia, but the aetiological role of *Candida albicans* and of various bacteria is still undecided. The purpose of this communication is to record the results of certain microbiological investigations. Interest has been particularly focused on the incidence of *Candida albicans* and various species of bacteria in chronic paronychia and the relationship between chronic paronychia and the presence of *Candida albicans* in other parts of the body.

Candida albicans in the nail fold.

The frequent presence of *Candida albicans* in chronic paronychia is well known, but the results obtained by different authors show considerable variation. For instance, Whittle *et al.* (1959) isolated *Candida albicans* from 41 out of 104 patients (39%) while Frain-Bell (1957) found an incidence of 70% in his series of 590 cases.

The present study comprised 34 cases showing the typical clinical picture of chronic paronychia; in 33 (97%) *Candida albicans* was cultured from the affected nail folds. Thus the incidence of *Candida albicans* in the present series was much higher than in the other two. There may be several reasons for this, but the selection of the clinical material and the techniques used in examination and culture might be the most important. In this study, only typical cases were included and I carried out all the investigations myself. The technique used in isolating the organism was as follows. A sterile orange stick moistened in normal saline was inserted deeply into the bolstered paronychial pocket and as much débris as possible obtained. This was immediately plated out on Sabouraud's dextrose agar and incubated at 22° C. for a minimum period of five days. Where several nail folds were affected only the most active fold was selected for culture. Another variable factor might be the state of activity of the nail fold infection at the time of examination. However, in 32 out of 33 cases *Candida albicans* was isolated at the first attempt and in the remaining case a positive result was obtained at the second. It would seem unwise to conclude that *Candida albicans* is absent merely on the basis of a single examination.

Candida albicans was identified in every case by its ability to form chlamydo-spores in cornmeal agar and by the fermentation of glucose and maltose with

the production of acid and gas. No change was produced in galactose or sucrose. Material from 27 of the patients was examined directly for mycelium and spores using liquor potassii and smears stained by Gram's method. Positive results were obtained with both methods in 9 instances, but in a further 9 only the Gram-stained preparations gave positive results. In the remaining 9 cases both methods yielded negative results. Comparing the two methods twice as many positive results were obtained with the Gram preparation. It should be recalled that positive cultures were obtained from all.

In order to determine whether there was any correlation between the state of the paronychia and the numbers of *Candida albicans* present, the nail folds of 14 patients were examined by a semi-quantitative cultural method. Débris obtained from the affected nail fold was mixed with a known volume of sterile saline and a standard loopful of this suspension spread over the surface of a Sabouraud plate in a uniform fashion. The plate was examined after 5 days' incubation at 22° C. and the growth of *Candida albicans* assessed as heavy, moderate or scanty. No consistent correlation could be shown between the state of the paronychia and the numbers of candida present: in some cases with very active paronychia only a scanty growth was obtained, while in others showing considerable clinical improvement cultures yielded a heavy growth. Too much significance should not be attached to these findings as the number of cases involved is small and the sampling error must have been considerable. The normal nail folds of a small number of patients with chronic paronychia were also examined for *Candida albicans*, but none was found. Similar negative results were obtained from 2 patients showing eczematous bolstering of the nail fold. These findings again concern very small numbers, but it is interesting to note that Whittle (1959) also failed to find *Candida albicans* in 20 patients with eczema or psoriasis involving the nail fold.

Candida albicans in interdigital clefts.

Because of the high incidence of *Candida albicans* in chronic paronychia it was felt that investigation of the interdigital clefts of these patients for *Candida albicans* might prove interesting. Accordingly the interdigital clefts of 29 patients with active paronychia were examined: *Candida albicans* was cultured from 9. It should be stressed that the skin of these clefts appeared quite normal and in only one patient was a past history of erosio interdigitalis blastomycetica obtained. In two cases *Candida albicans* was found only in the clefts adjacent to the paronychia and a local "spill-over" would seem to be the most likely explanation. However, in 4 patients with bilateral paronychia *Candida albicans* was isolated from the clefts of one hand only: in yet another patient *Candida albicans* was recovered from the interdigital clefts of the normal hand, but not from the clefts of the affected hand. In spite of these

rather inconsistent findings the most likely explanation would seem to be contamination from the affected nail folds. *Candida albicans* was not found in the interdigital clefts of 2 patients suffering from eczema of the fingers.

Bacteria in the nail fold.

The bacterial flora of the affected nail folds was also studied in these 34 patients with chronic paronychia. Material from such a fold was inoculated on plates containing blood agar, 6% blood agar and MacConkey's medium, and the organisms were identified after incubation at 37° C. for 18–48 hours. The results (Table I) show that *Escherichia coli* was the predominant organism (29), while *Proteus vulgaris* (20), enterococci (10) and other intestinal organisms were frequently found. Other bacteria isolated included *Staphylococcus aureus* (7), coagulase negative staphylococci (14) and diphtheroids (18). The latter are well recognized as predominant members of the bacterial flora of normal skin. *Staphylococcus aureus*, coagulase negative staphylococci and enterococci were also recovered from nail folds of the 2 patients with eczema.

TABLE I.—*Bacteria Isolated from 34 Patients with Chronic Paronychia.*

Species.	Number of Patients.
<i>Escherichia coli</i> . . .	29
<i>Proteus vulgaris</i> . . .	20
Enterococci . . .	10
<i>Klebsiella aerogenes</i> . . .	7
<i>Pseudomonas pyocyanea</i> . . .	4
Paracolon bacilli . . .	3
<i>Staphylococcus aureus</i> . . .	7
Coagulase negative staphylococci . . .	14
Diphtheroid bacilli . . .	18
Miscellaneous . . .	2

The source of the intestinal bacteria in paronychia.

It is evident from the foregoing that the bacteria most frequently isolated from the paronychial nail folds belong to the intestinal group and the most likely conclusion would be that these originate from the gut. This point would be made a little more specific if it could be shown that the strain of intestinal organism present in a patient's nail fold was the same as that in his faeces. *Proteus vulgaris* appeared to be a suitable organism for this purpose, because it is present in the faeces of about one third of healthy people and a simple and accurate method of typing strains of *proteus* was readily available (Cunliffe and Krikler, 1953). Accordingly, cultures were made from the faeces of 18 patients with paronychia; *Proteus vulgaris* was recovered from fifteen. Typing was possible in 12 instances and in 10 of these the strain from the nail fold appeared identical with that isolated from the gut. In only 2 cases were the strains dissimilar.

Thus the nail folds are not only frequently infected with intestinal organisms, but there is evidence to suggest that they are infected from the intestine.

Candida albicans in the gut.

Transference from the gut is also a possible route for infection with *Candida albicans*. Rectal swabs were therefore taken from 18 patients with paronychia, preliminary inoculation being made in a liquid potato extract medium and on Sabouraud plates containing aureomycin in a concentration of 10 μ g per ml. *Candida albicans* was recovered from nine. In 17 of these patients similar cultures were also made from the mouth with positive results in thirteen. Thus *Candida albicans* has been found in 50% of the rectal swabs and in 75% of the mouth swabs. If actual specimens of faeces had been examined rather than rectal swabs it is likely that a figure higher than 50% would have been obtained. It is likely also that in some persons the excretion of *Candida albicans* is intermittent. Therefore, unless repeated examinations are made, misleadingly low results may be obtained. Recent workers (Winner, 1959) have indicated that *Candida albicans* can be recovered from the gut in a high proportion of normal persons provided a sensitive technique is used. If this is the case, potential sources of infection for the nail fold are available in the mouth and faeces. This could best be proved by showing that identical strains of *Candida albicans* were present in the nail fold and gut. Unfortunately no method of typing is at present available.

Whittle *et al.* (1959) found that the right middle finger was the site first affected and made the point that in right-handed subjects this would be the finger most likely to be contaminated after defaecation. Frain-Bell (1957) also noted that the right middle finger was the one most frequently affected in chronic paronychia. In the present series not only was the right middle finger the first site affected, but it was also the most frequently involved. Five patients known to have *Candida albicans* in the gut were treated with oral Nystatin in a dosage of 500,000 units t.i.d. for several months but no dramatic improvement in the state of their paronychia was seen. Such a result is not really surprising as it is doubtful whether the course of an established paronychia would be much influenced by eliminating the source of infection.

Although the vagina might be a source of infection of the nail fold, Whittle *et al.* (1959) found *candida* in only 1 out of 18 cases. In my series, only 5 out of 20 patients complained of any vaginal discharge and in none of these was there evidence of vaginal moniliasis.

SUMMARY AND CONCLUSIONS.

The mycological and bacteriological findings in 34 cases of chronic paronychia are reported. *Candida albicans* was cultured from the affected nail folds in

97% of patients, a much higher incidence than in other reported series. Possible reasons for this are given.

A predominant feature of the bacterial flora of the nail fold was the high incidence of intestinal organisms. Evidence that these organisms originated from the patients' gut has been produced by finding identical strains of proteus in the nail fold and faeces.

In patients with chronic paronychia *Candida albicans* was isolated from 75% of mouth swabs and 50% of rectal swabs. Although absolute proof is lacking, it is postulated that the mouth and faeces frequently provide a reservoir of *Candida albicans* from which the nail fold is infected.

I would like to express my thanks to Dr. Sidney Thomson and Dr. David Williams for referring cases to me; to Dr. A. C. Cunliffe for affording me laboratory facilities and for much helpful advice during the preparation of this paper.

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THE TREATMENT OF RINGWORM WITH GRISEOFULVIN.*

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GRISEOFULVIN was first isolated by Oxford, Raistrick and Simonart (1939) as a metabolic product of *Penicillium griseofulvum*. Grove and McGowan (1947) showed that the antibiotic "curling factor" isolated from *P. janczewskii* by Brian, Curtis and Hemming (1946) was identical with griseofulvin and it is now known that certain other species of *Penicillia* are also capable of producing this antibiotic. Brian (1949), who studied the biological activity, showed griseofulvin to be fungistatic to most mycelial fungi and systemic antifungal activity in plants was demonstrated by Brian, Wright, Stubbs and Way (1951).

Although it is effective in low concentrations against dermatophytes *in vitro*, griseofulvin has proved no better than orthodox preparations when applied topically to ringworm lesions (Williams, 1957; Peterkin, 1958). However, when administered orally to animals, even in very high dosage, griseofulvin shows a remarkable absence of acute toxicity. Single oral doses have failed to kill mice at a level of 50 g./kg. or rats at 10 g./kg. (Tomich, 1958). Since it is only sparingly soluble in water and since there was no satisfactory assay for griseofulvin in blood and body tissues at the time when these toxicity trials were done, it was believed that this absence of toxicity was probably explained by negligible absorption from the gut. In view of the very obvious need for a new therapeutic approach to dermatophyte infections however, it seemed well worth while carrying out some preliminary trials to investigate the effect of oral griseofulvin on ringworm infections. In a preliminary report (Gentles, 1958) it was shown that oral griseofulvin rapidly cleared artificially induced ringworm in guinea-pigs and this has been followed by reports illustrating its undoubted efficacy in the treatment of ringworm infections in man (Williams, Marten and Sarkany, 1958; Blank and Roth, 1959; Riehl, 1959) and further reports of its use in animal trials (Lauder and O'Sullivan, 1958; Martin, 1959).

ANIMAL STUDIES.

At first, griseofulvin was administered in suspension to guinea-pigs infected with *Trichophyton mentagrophytes*. Treatment was begun on the day of infection and given daily at the rate of approximately 200 mg./kg. body weight for 10 days. The treated animals did not develop ringworm. Similar results were obtained when the treatment was delayed until 4 days after infection and the daily dose was reduced to approximately 75–100 mg./kg. body weight.

* Based on a paper read at the Thirty-Ninth Annual Meeting of the British Association of Dermatology in July, 1959.

Following on these encouraging results a large group of animals was infected with *Microsporum canis*. Treatment of half of them was commenced on the tenth day when the infection was well established and although the lesions had not reached the inflammatory stage, infected hairs were fluorescent under Wood's light. Griseofulvin was given daily in tablet form at the rate of approximately 60 mg./kg. Within 4 days the beneficial effect of treatment was clearly evident; the control animals,



FIG. 1(a).

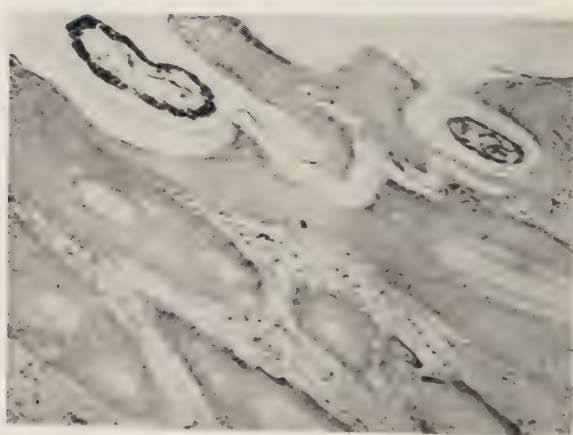


FIG. 1(b).

FIG. 1.—Skin sections: 14-day *Microsporum canis* infection in guinea-pig. (a) Untreated. (b) Treated with oral griseofulvin for 4 days, 60 mg. kg. daily. ($\times 135$.)

which had received blank tablets, had highly inflammatory lesions whereas the lesions on the animals receiving griseofulvin had markedly regressed. At this time and also 4 days later, on the 18th day after infection, skin sections were taken from some of the animals in each group. These revealed a marked reduction in the number of infected hair follicles in the treated group compared with the untreated (Fig. 1). Infected hairs in both treated and untreated groups of animals continued to fluoresce under Wood's light and about 7 days after the first treatment it was noted that in the treated group the fluorescence was clearing from the base of the hairs. Microscopic examination of epilated hairs showed that the fungus was confined to the

fluorescent portion and was sharply delimited from the uninfected basal part of the hair. This restriction of the dermatophyte to the upper part of the hair shaft was also seen in certain of the skin sections from animals after 4 treatments with griseofulvin: comparable sections from animals in the untreated group showed dermatophyte hyphae present down to the level of the nucleated zone (Fig. 2). An obvious explanation of this finding was that the griseofulvin was present in the portion of the hair which had been formed during treatment and had thus rendered it resistant to fungal invasion. Evidence to support this hypothesis was obtained by careful

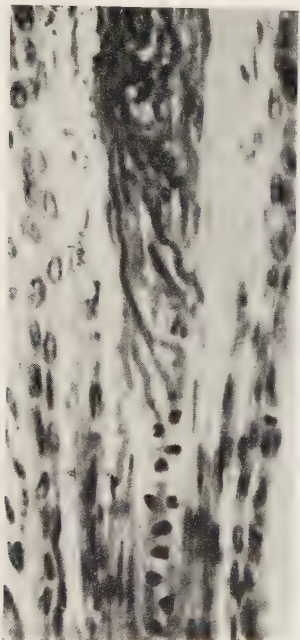


FIG. 2(a).



FIG. 2(b).

FIG. 2.—Guinea-pig hairs infected with *Microsporum canis* cut longitudinally in skin sections. (a) From untreated animal. (b) From animal treated with oral griseofulvin for 4 days, 60 mg./kg. daily. ($\times 650$.)

examination of skin sections and epilated hairs of treated animals. In certain of these, the characteristic malformation produced by griseofulvin on the hyphae of susceptible fungi was noted (Fig. 3).

Further evidence of the presence of griseofulvin in hair of animals after oral treatment was subsequently obtained by Gentles, Barnes and Fantes (1959). The hair of a group of albino guinea-pigs was clipped close to skin level and the animals treated daily with 30–40 mg./kg. of griseofulvin for 23 days by which time the hair had regrown to a reasonable length. Precautions to prevent contamination of the hair by urine or faeces were observed. Bio-assay revealed griseofulvin to be present in the hair of treated animals at a level of about 6 μ g. per gram of hair. None was detected in the hair of untreated animals. Since about half of the griseofulvin was extracted from the hair by cold water and the remainder by boiling methanol it seems likely that it was present as a deposit and was not chemically bound to the keratin.

The pattern and the relatively short duration of the artificially induced infection in guinea-pigs limits the information which can be obtained in trials with these

animals. Nevertheless, it was obviously necessary to find out if daily doses of less than 60 mg./kg. would clear infection and also to discover how frequently doses must be given and for how long. Since the infection was cleared almost entirely from the hair follicles after 8 daily treatments of 60 mg./kg., this period was chosen.

Eight daily doses of 30 mg./kg. were found to be completely effective and daily doses of 15 mg./kg. also halted the progress of infection as shown by the clearance of fluorescence from the base of the hairs and the absence of inflammation. However, on the latter occasion re-infection from fungus present in the distal parts of the hair took place after treatment was stopped.

To investigate the effect of varying the frequency of dosing, three groups of animals were given the same total amount of griseofulvin. The first group was given



FIG. 3.—Skin section showing "curling" of fungal hyphae in guinea-pig hair infected with *Microsporum canis*. Oral griseofulvin for 2 days, 60 mg./kg. daily. ($\times 650$.)

a single dose of 120 mg./kg. on the 10th day after infection: the second group 2 doses of 60 mg./kg. on the 10th and 14th days and the third group 4 doses of 30 mg./kg. at intervals of 48 hours starting on the 10th day. The course of the disease in the animals which received the single dose was not noticeably affected. The lesions on the animals which received 2 doses were slightly less inflammatory than those of the controls but the infection persisted until the time of spontaneous cure in untreated animals. In the animals treated at 48-hour intervals, the infection cleared rapidly and completely without development of inflammation. Thus 120 mg./kg. griseofulvin cleared established *M. canis* infection in guinea-pigs when given in 4 doses of 30 mg./kg. at 48-hour intervals, halted invasion of tissue, but allowed reinfection to occur when given in 8 daily doses of 15 mg./kg. and was ineffective when given in 2 doses of 60 mg./kg. or a single dose.

DISCUSSION.

All common dermatophytes are sensitive to low concentrations of griseofulvin *in vitro* and it is now known that in humans, infections with *T. rubrum*, *T. mentagrophytes*, *M. canis*, *M. audouini*, *E. floccosum* and *T. sulphureum* respond

to oral treatment with griseofulvin (Williams *et al.*, 1958; Blank and Roth, 1959; Riehl, 1959) as do those caused by *T. schoenleini* (Fergusson, 1959; Mitchell, 1959; Cochrane and Tullett, 1959), *T. violaceum* (Williams, 1959; Neves, 1959) and *T. concentricum* (Gurd, 1959). Although sparingly soluble in water, griseofulvin is obviously rapidly absorbed from the gut and it has recently been shown (Bedford, Child and Tomich, 1959) that in man, blood levels of griseofulvin are related to dose.

Keratin formed during treatment is clearly resistant to fungal invasion and there can be little doubt that this resistance results from the deposition of griseofulvin in the keratin. Griseofulvin has been extracted from hair of treated animals. Although, during the process of arthrospore formation in the fully keratinized part of the hair, the hyphal form can easily be confused with griseofulvin-affected hyphae, "curling" undoubtedly occurs to a limited extent in hair of treated animals. It has never been seen however, in specimens of skin and nail from treated humans despite careful examination of large numbers. Since the "curling" effect is evident *in vitro* only in the strongly growing hyphae which actually penetrate, or are in close contact with, the substrate containing griseofulvin, it seems probable that, in keratin, growth is generally too slow for "curling" to take place and the presence of griseofulvin in the keratin completely prevents entry of the fungus. Theoretically it is probable that once a barrier of resistant keratin has been formed, treatment may be stopped and the continued outgrowth of resistant keratin will cast off the infection. The duration of treatment required for a cure will therefore depend to a large extent on the rate of keratin production and is likely to vary with the animal, with the part of the body affected and with other factors influencing keratin formation. Animal studies indicate that the length of treatment which must be carried out is related to the dose level and will also depend to some extent on the duration of the infection and susceptibility of the host. By the tenth day, *M. canis* infections in guinea-pigs are well established but still at an early spreading stage of development and are more difficult to cure than older inflammatory infections which are already tending towards spontaneous remission. Although in guinea pigs, daily doses of 15 mg./kg. allowed reinfection to occur, this would probably have been prevented if treatment had been continued for a period of more than 8 days. In certain cases of cattle ringworm, Lauder and O'Sullivan (1959) found daily doses of 15 mg./kg. adequate when treatment was given for 21 days and in guinea-pigs also this dose was obviously sufficient to halt invasion of tissue.

Treatment has so far been given in most cases daily although it is indicated from animal studies that doses may be given at 48 hour intervals. However, Fantès (1958) was unable to detect griseofulvin in blood of calves 48 hours after oral administration and this interval of dosing probably approaches the upper limit.

Although it is known that mere exposure to a dermatophyte does not mean the establishment of the disease, the conditions which predispose to infection are as yet incompletely understood. Griseofulvin is fungistatic, not fungicidal and all infected keratin which is shed will contain viable fungus. Isolates have been obtained in this laboratory of *M. canis* and *T. sulphureum* from hair of individuals after 3-4 weeks of oral treatment with griseofulvin, of *T. schoenleini* after 3 months, and of *T. rubrum* from nails after 4-5 months' treatment. Hundreds of colonies of *M. canis* and *M. audouini* have been isolated from berets of persons being treated for scalp infections with these fungi. Obviously large quantities of viable fungus which will be a potential source of reinfection will also be present on the scalp and hair and in socks and shoes. Until the full extent of this hazard is understood it would seem that the only method of treatment with oral griseofulvin which can be used with complete confidence is to continue therapy until the fungus can no longer be detected by microscopy or culture. This is obviously over-treatment and there are many instances known of cures resulting from treatment which, either by accident or design, has been far short of these requirements. However, before griseofulvin can be used to full advantage a great deal more information is necessary. Much of it must come from clinical trials in which the progress of the same form of infection can be compared with variations of treatment. The treatment for anthropophilic infections is unlikely to be the same as that required to clear those caused by zoophilic dermatophytes and the treatment of scalp ringworm will obviously differ from that used for nail infections. There must also be further investigations into the relationship between dosage and blood level and between blood level and keratin content of griseofulvin. The optimum dose may not be merely the minimum amount of griseofulvin which will render keratin resistant to invasion and although quite small doses are at present being used with good results, it is possible that larger amounts over a shorter period of time will prove more efficacious; a total dose of x grams given at the requisite level and at the right time might well do the work which would otherwise require $2x$ grams. Careful mycological investigation, together with a high standardized criterion of cure will in time produce useful information regarding susceptibility and reinfection.

A considerable amount of work has already been done and information on a number of these important factors should soon be available. Meantime, griseofulvin continues to be used with good effect and without evidence of any serious toxic reactions. There are no reports as yet of the occurrence of resistant strains of dermatophytes and it is hoped that this problem will not arise.

I am indebted to the many clinicians and friends who have discussed with me the numerous problems of griseofulvin and treatment of ringworm infections. In addition to those whose personal communications are noted in the text I should like to thank Drs. Mary S. Smith, J. G. Holmes and J. C. P. Logan. I also wish to thank Miss C. O. Dawson who assisted with much of the

laboratory investigation and Misses E. Brown and M. Mennie for technical assistance. The griseofulvin for these studies was supplied by Glaxo Laboratories Ltd.

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GRISEOFULVIN.*

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ONCE upon a time—and thus all good stories begin—there was an old retired general practitioner who said that he could treat all skin diseases although he could diagnose none. Those were the slap happy days when local treatment was a magnificent pseudo-science—not that even now do we have much understanding of how local applications work—and internal treatment was a desperate matter of letting justice seem to be done, not too critically. Perhaps there were some grounds for the regular stock gibes at the skin doctors whose patients never died and never got better—although one has a sneaking feeling that more of other people's patients never got better and certainly more died. But in the last fifteen years there have been remarkable advances in the chemical and antibiotic field. Treatment is becoming so specific that there is much to be said for a proper diagnosis before starting it. Penicillin has made syphilis so rare that it is easy to forget its existence. Anti-tuberculous drugs have ruined for us a fascinating, a lovely group of dermatological conditions. And now griseofulvin.

The fungi which cause ringworm in man live and multiply in what is virtually dead tissue ; they live in, feed on and distort keratin. Things become dangerous for them when they suicidally excite an inflammatory reaction by which they will be cast off or by which the nature of the keratin may be altered and made inhospitable. The milder the reaction to the presence of a fungus the more chronic the infection. It is not a simple matter to get local applications into keratin and those which seem to succeed in curing fungus infections do so because of the inflammatory reaction they produce. Many of us used griseofulvin both in ointment and paint vehicles two or three years ago and it was found wanting. Local treatment, therefore, is not very logical. One day someone will discover what it is in keratin which divides us into catchers and non-catchers of fungus infections. It has long been a pleasant phantasy to imagine one's self being able to make any susceptible keratin hostile to fungi simply by feeding an appropriate substance to the patient. Griseofulvin, for the moment at least, is the only preparation which can somehow or other act in some such way. Given by mouth it seems able to get into those cells which will ultimately form keratin and gives them, even when they become keratinized,

* Based on a paper read by Dr. Williams at the Thirty-ninth Annual Meeting of the British Association of Dermatology in July 1959.

the power to prevent their penetration by fungi; so that in due time the organisms are cast off along with the scales shed from the skin or in the shed parts of the nails or hairs, all of which are replaced by clean tissue. Whether the substance finding its way into keratin is griseofulvin itself or a breakdown product or some compound with a substance already present in the body is not known.

You have heard from Dr. Gentles something of the history of griseofulvin and its development. His modesty has led him to play down the important part he himself has taken in all this fascinating story, dating back to before the war. It was, then, in the late summer of 1958, that the evidence acquired in animal and other laboratory studies was considered sufficient to suggest that griseofulvin might be of value in the treatment of fungus infections of the skin, scalp and nails of man. Toxicity experiments carried out over a long period seemed also sufficient to show that griseofulvin could be used in the human subject with safety. This we say despite the paper of Paget and Walpole (1958), published in November showing that the drug had a vicious antimetabolic effect, rather like that of colchicine, on the bone marrow, intestine and seminal epithelium: but they had given very large doses intraperitoneally and intravenously to rats. There was among many people an understandable anxiety, therefore, about using griseofulvin but not enough appreciation of the size of the dose and the route used by Paget and Walpole. On the other hand, Tomich (1959) had carried out tests over a long period—tests which have now been much extended—on rats and guinea-pigs. After taking doses of griseofulvin two to four times as large as those mostly given to man, rats showed after four months no impairment of fertility and at five and twelve months no significant blood abnormality. Guinea-pigs fed on the drug for twelve months also showed no blood changes that mattered and post mortem findings were no different in treated and control animals.

The therapeutic prospect was then exciting but with the feeling that too much must not be expected the trial was begun with marked scepticism. Experience so far has been so gratifying that it is difficult to be restrained about what seems to be happening. But even now we must force ourselves to recognize that there is much to be learned, for example concerning dosage and side effects, apart from fundamental information about the metabolism and mode of action of griseofulvin. What we have to say about the findings at King's College Hospital must, I think, still be looked upon very much as a preliminary communication. Our experience, as you will hear, is still slight. We have started treatment on only some hundred and twenty cases of fungus infections and when broken up into their groups they seem very few. At least they may serve as a basis for discussion.

Our trials began in October 1958. Although tempted to try several dosage schemes, it seemed wise at first to administer griseofulvin to a sufficient number

of patients in what was estimated to be sufficient dosage and to continue treatment right up to the time of cure, even though this might be a matter of months. Thus we might be able to produce a base line on which—to mix metaphors—variations could later be played. As with some better known variations, the best scheme of treatment for the different infections will for some time remain an enigma. Statistical control fortunately for those of us who do not understand arithmetic did not seem to be needed since either the patients would get better or they would not and at the same time the fungi would disappear or they would not. It was indeed a pleasant thought to contemplate a trial where impressions would count for nothing and the end points would be clear cut. We have treated most cases with $\frac{1}{2}$ g. of griseofulvin twice a day—some with 1 g. twice a day. It may well be that 2 g. a day are needed to cure certain types of case. We have in the main deliberately avoided local treatment in this trial except in cases of scalp infections.

Now we find it difficult to know how best to present our results so far, since they are concerned with so many parts of the anatomy and with various species of fungi. Since most of the cases are—or in some cases were—infections by *Trichophyton rubrum*, perhaps we could first deal with that fungus and split up the results on an anatomical basis. Most of the cases, of course, had infections of many areas. Treatment has been started in 50 cases from which *Trichophyton rubrum* has been grown: there are another 19 cases which clinically suggest a similar infection with, so far, negative cultures, but positive microscopic findings. It is interesting how often positive cultural findings are not made until several searches have been made as the weeks go by. The motto of the good mycologist is always "if at first you don't succeed, try, try again". We have no doubt that most of those cases with negative cultural findings will be found to be positive before long, since most are early in their treatment. Of these 69 cases, only 11 had infections of less than 5 years' duration: another 25 of less than 10 years, another 20 of less than 20 and the rest had been infected for 20 years or more, the record being 50 years! Cure, incidentally, does not seem to be related to duration of infection in this group.

Let us now consider what happened to infections of the palms by *Trichophyton rubrum*: 22 patients with rubrum infections of the palm have been started on treatment; 5 were normal clinically and microscopically in a month, 11 in 2 months, and 4 in 3 months. One of these showed positive microscopic findings even at ten weeks, although he was clinically and microscopically clear two weeks later and has remained so for several months. You must realize that most of these patients are still taking griseofulvin because they also have nail infections. Another patient still shows the fungus after three months but he has had two gaps of at least a fortnight each during which he could not get to the clinic. The last patient is only a new boy and insufficient time has passed to make any proper assessment. Itching, when it

exists, soon ceases on these palms and sweating returns, sometimes after years of absence ; many of these patients are, of course, ichthyotic and don't sweat anyway. Four cases of suspected but not proved *T. rubrum* infections behaved in just the same way.

Next, to finger nails. The rate of cure will depend obviously not on the extent of the nail involvement, but on the rate of growth : I do not know whether infection itself slows the rate of growth. Of 26 cases with proven *T. rubrum* infections, 10 now have normal finger nails after periods of treatment varying from 3 months to 7½ months. The three-month case is the only one in the series treated by preliminary avulsion of the nails. Avulsion might be an economy, but it is certainly the most barbaric way to treat nails. Most cases take five to six months to get well, which, after all is what would be expected. Fungus was found under the microscope as late as the fourth and fifth months in several of these cases. Once a nail is clinically completely normal, microscopy and culture have always been negative. Twelve cases are showing steady improvement and two are nearly well at five months. In one case, two finger nails improved while the thumb is unchanged or worse at three months. We wonder whether some other organism may be concerned but such an organism has not yet been found. The last case is of particular interest and importance. He was treated for only one month after which time he went abroad. Six months later two finger nails were quite normal while the thumb was still clinically and microscopically positive. This suggests to me that it is only a fond hope to believe that a short course of treatment will be followed months later by cure. That such a thing might happen is true—indeed we believe it has happened—but the chances of reinfection of the proximal parts of the nail from the growing out infected parts must be very high. We also believe that microscopical finding of a fungus means viability of the fungus in these cases. Treatment must be continued until the last remnant of distorted nail has been cut away. Whether treatment has to be given daily is another matter. Seven cases with clinical and microscopic but not cultural evidence of *T. rubrum* infection are behaving in the same way.

If you can endure more figures, may we now consider the soles ? Thirty-eight patients with cultural evidence of *Trichophyton rubrum* infection in at least one of their involved areas have been treated for sole infection. All were, of course, microscopically positive. Nearly all had at the same time an infection of the toe nails and are continuing treatment. You will see that we are not quite as speedy as some others in curing our patients. Ten patients had positive scrapings at six to eight weeks, seven proceeding to apparent cure later. The other three are still at the six week stage. Yet another was positive at ten weeks and another positive at nineteen weeks although she was clinically normal ! One was positive at nine weeks after slightly erratic treatment.

Another treated for only a month was still showing *T. rubrum* at four months and still positive after another ten weeks of treatment with 1 g. a day. On the other hand, someone treated for only a month was clear seven months later : so far only *Scopulariopsis brevicaulis* has been grown from his toe nails. Finally, one patient with the typical snowstorm of *T. rubrum* filled scales on only one sole was clear after two months' treatment and remained so two months later. He had no nail infection, which is a little curious. If one judges cure by complete disappearance of the tell tale scales and inability to find a fungus, then we judged only two cases to be well in five weeks, ten in from six to eight weeks, and nine in from nine to twelve weeks. The rest of the cases have had much shorter periods of treatment. It seems then that it is difficult to find the fungus after six weeks and cure follows in two to three months, but not in everybody quite as quickly as that. It would be nice to know how long it takes the uninfected epidermis or horny layer to grow from bottom to top. If these results are anything to go by, it must be about eight weeks.

Toe nails we can cover more quickly : 41, that is to say most, of the culture-positive patients had nasty toe nails and eight of the suspected but not proved *T. rubrum* cases. None of these patients yet has clear toe nails—which is not surprising, since as Ovid said, "*Temporis ars medicine fere est*", which for the benefit of the member from Cambridge where they no longer have to learn Latin, we will translate—the art of medicine is generally a question of time—and it seems to take a very long time for toe nails to grow their full length. Indeed, we have been driven to wonder in our exasperation with them whether infected toe nails grow out even slower than the normal. The best we can report is four patients with nearly normal nails, one after seven months and the others after eight months of treatment. Please note that one of these had a positive culture at eight months and another at six months. We must say that it does seem to be more difficult to grow the fungus as the months go by, even though it can be seen under the microscope. Twelve others with at least three months' treatment are obviously improving. On the other hand, six treated for at least three months are no better, one of them having reached the seven month mark with a positive culture at five months. There is one very curious patient who had *T. rubrum* infection of the toe nails of both feet : after seven months of treatment the nails of one foot—originally the worse—are very nearly well while those of the other foot are more grossly affected than when he started treatment. Is there a hint in this that griseofulvin will not cure 100% of patients—and it is expecting a bit much to imagine that—or have we been giving too small a dose ? Most of these stubborn creatures have been taking one gram a day ; we think that perhaps we should advise double that dose for resistant cases. On the brighter side, one patient took griseofulvin for barely a week—she suffered all the imaginary complications possible, including the fact that she worked for a drug firm of continental origin, and

the drug was stopped. Six months later her nails were nearly normal! Her soles, however, were still grossly infected. The eight negative culture cases follow very much the same pattern.

We turn next to the interdigital clefts of the feet. Here we are in difficulties since the trial began in the early winter months when cleft fungi, like Caesar's legions, retreat into winter quarters, and are difficult to find and unpredictable in their behaviour. We, therefore, tended to avoid clefts in the early days. There are only ten cases to report with proven *Trichophyton rubrum* infections: all had infection elsewhere, including in every case but one the toe nails. Of these six were microscopically positive at 3, 6, 10, 11, 12, and 16 weeks and 7 months and continue under observation. Another appeared to be clear at one month and remained so at six months; another was clear at nine weeks after a positive test at three weeks; one was positive at 20 weeks after a gap in treatment of two months and who had infected nails. Finally we stopped treatment in one patient after five weeks with normal clefts and no blisters on her sole and we wait to see what happens. There is just a suggestion here that it may be more difficult to root out the fungus from a warm, moist, comfortable home between the toes than from the wide open spaces of the soles. This indeed may be one of the real testing grounds, clinically and in the back rooms.

We have treated five patients with *T. rubrum* infection in the groins, buttocks and on the elbow. These all responded readily and were well in less than a month. So much for *Trichophyton rubrum*: the remarkable effects of griseofulvin on cases infected by this fungus can best be measured by the immense delight and the happy smiles on the faces of patients who now see cure in sight after many years of being frightened to shake hands lest they spread infection and who no longer will need to be self-conscious about their finger nails.

Trichophyton verrucosum is a rare visitor to the clinics of London and our experience is limited to one case—and he was cleared up very quickly. From what we have heard from others this might perhaps be a less satisfactory infection to treat. Local treatment alone will, of course, often suffice: would a combination of griseofulvin with local treatment be any better? We are sure there must be those here who can tell us what they think on this point and on whether a bigger dose of griseofulvin might be the answer.

We have treated only one case of *Trichophyton sulphureum* infection of the skin of the neck. He was well very quickly.

Epidermophyton floccosum appears three times in the series. A sole infected with this fungus was probably well in ten weeks and certainly well in five months. Another patient had infection of her soles which recovered in two months at the most and of the finger nails and toe nails which are growing out well after six months' treatment. The third is one of our star cases with a

26 year history of gross hyperkeratosis of both soles. The fungus was found regularly up to the end of the third month of treatment which was stopped after five months when the soles were clinically normal. At seven months there was no recurrence.

As a bit of gamesmanship we mention the patient with one big toe nail discoloured in a curious, yellow fashion from which only *Scopulariopsis brevicaulis* has been grown on three occasions in two months. This organism's significance as a pathogen is a matter of debate and it is not very sensitive to griseofulvin in the test tube. However, his nail is perhaps beginning to show signs of improvement after only two months of 1 g. a day. This attractively named fungus—A. P. Herbert ought to write a poem about it, it scans so nicely—has materialized in two other patients' nails, one with *T. rubrum*, the other with *T. mentagrophytes*. Probably a contaminant, Dr. Gentles thinks.

Most of the reports say that pityriasis versicolor does not respond to griseofulvin, although Pardo Castello claims to have cured two cases. Our four cases laughed at the drug, with no response at all.

In seventeen cases *Trichophyton mentagrophytes* was found. In nine, the soles alone were affected. It must be realized that fungus can be found fairly easily until the last bit of scale of the last blister is shed, which takes about a month. Two other patients with concomitant nail infections also had infected soles. Of the eleven cases, eight were quite well in four to six weeks. The other three are about to be cured, we believe. Five patients have infected nails, sometimes finger nails alone, or toe nails alone or both. They all seem to be improving, the longest having been treated for four months. The last case has grown only *Scopulariopsis brevicaulis* from a toe nail, although he had *T. mentagrophytes* on the soles; his nails are no better after five months.

Two cases had what could be fairly called "id" eruptions on the hands. These disappeared very quickly. It is nice to think that we might now be able to test very properly the theory of "ids" and their relationship to fungus infections in other sites, but just as we hope that every bit of maceration between the toes will not be treated by griseofulvin since so often the cause is not a fungus, so we hope that every eczema or blistering eruption on the hands is not going to be similarly treated on the wild assumption that there might be a fungus lurking somewhere.

We must mention one patient perhaps more of mycological than of pure dermatological interest. He had lichen planus, pityriasis versicolor and clinical ringworm between the toes. From this last area *Trichophyton persicolor* has twice been grown. This fungus is often regarded as a variant of *Trichophyton mentagrophytes* but after treatment for five months with griseofulvin, 1 g. a day, there is no improvement and the fungus can still be grown. Perhaps this is a little evidence that it may be a species in its own right.

And now we come to the hair. Our experience is so limited, we are almost ashamed to refer to it. Vast series of cases are being treated in the United States, so that our lot seems very puny. They number only 11, five infected with *Microsporum canis*, three with *M. audouini*, two with *T. sulphureum* and one with *T. violaceum*. This last one with *T. violaceum* is the most interesting since her infection had been present for four years, scorning thallium and x-ray epilation twice. She was well in a month and is growing a pretty good head of hair five months later. Favus of the scalp and of other areas responds just as well, but we have treated none. Treatment of scalp infections requires either a highly intelligent mother or admission to hospital. Probably 1 g. a day is the right dose, but to think that griseofulvin with no local toilet or treatment will effect cure is to court failure—as we found in our early cases. At the moment we think it is right to use something like Whitfield's ointment daily and to shampoo the scalp daily, in order to deal with odd spores lurking about the scalp which might persist when drug treatment is stopped. With small-spore infections we have simply shaved or cut off the infected hairs when their fluorescing and therefore infected distal parts have grown clear with non-fluorescing hair appearing beneath. This takes about three weeks. It is interesting to see how the brilliance of the fluorescence fades and becomes a greenish colour, although the hair is still infected with viable fungi. Routine advice about destroying or sterilizing head gear, brushes and combs and so on is perhaps too obvious to need mention—but we forgot it in the excitement of treating the first cases. It is, of course, theoretically possible for a single dose to be followed by a cure.

We have already mentioned the early anxiety about toxic effects. If one treats 120 patients over periods up to eight months it is likely that during that period some at least will suffer from intercurrent disease, and as far as we know, griseofulvin endows its takers with no immunity against other infections food poisoning, hangovers, or headaches. With this drug as with all others it is so difficult to know when disturbances of the general health are due to the drug, to coincidental causes or to the imagination. We can but tell you what the patients told us and you can discount what you will. We think we can fairly say that although some of our patients have been upset during the period of treatment with griseofulvin, in no case has it been possible to be sure that the upset was not due to some other cause, with the exception of headaches. Eight patients did have headaches early in treatment which they and we blamed on to griseofulvin but the headaches disappeared within a week. Two patients complained of thirst and each of the following complaints happened in a different patient, feeling dopey, irritability, weariness, feeling queer, sickness for a day or two, looseness of the bowels: we could probably do better than that from the congregation in this room. We saw a toxic erythema in a patient on griseofulvin who developed tonsillitis, but no rash when the drug,

which we withheld, was again given. One patient developed severe and continued diarrhoea which persisted for at least a month after the drug was stopped. More important than all these is the patient who thought she might have become pregnant—her periods were erratic—and proved the point almost as quickly as the laboratory by aborting. Is this any indication not to give griseofulvin in pregnancy? We don't know: experimental animals are not likely to abort when on the drug. Sensitivity to penicillin is, of course, no contraindication to taking griseofulvin: there is no chemical relationship between the two antibiotics. We come now to the question of possible effects on the blood. We think that the only thing of which we are sure is that we do not know enough about normal blood counts, how low they may go and still be considered normal and how much the total and differential count may vary from day to day or from hour to hour. What, for instance, is the significance of a total white cell count of 2800 and 55% neutrophils in a patient before treatment and a normal count two weeks later? This is a more frightening count than any patient produced after treatment. Over ten thousand patients the wide world over have been treated by griseofulvin in daily doses even above 2 g. and no serious blood dyscrasia has yet been reported to the manufacturers. Agranulocytosis such as occurs with N.A.B., the sulphonamides or chloramphenicol has not been seen and routine blood counts anyway never pick up this so sudden tragedy. Sometimes we wonder whether there is a different, transient effect more marked in the first fortnight of treatment which lowers the white cell count and perhaps the haemoglobin but from which recovery is complete even though the drug is continued. We have not had the courage to do regular sperm counts or testicular assays on our patients: in a less inhibited and even more litigious minded country these have been done, we understand, and no abnormalities found.

We have now done, feeling very much that what we have said is very disjointed with many loose threads spoiling the half finished tapestry. That griseofulvin is a remarkable drug with minimal toxic effects and that it has come to stay, we have no doubt. We must now move on from the initial period of excitement to that of fuller assessment and the problems which await us will keep dermatologists, mycologists and pharmacologists happy for years. What is the right dose, how often should the dose be given? Will the fungi cunningly adapt themselves to their new enemy? What are the chances of reinfection or do patients in fact have an immunity which will prevent reinfection? What other diseases, if any, might it help to cure? What possibilities are there in slight chemical alterations in its molecule? Has it any effect other than antifungal? These and other problems await us. As Montgomery must have said, the break-through has been achieved and our forces can now pour through the gap to consolidate our gains.

Perhaps we could finish by quoting Puck :

“ If we shadows have offended,
Think but this and all is mended,
That you have but slumber'd here,
And this weak and idle theme,
No more yielding but a dream,
Gentles, do not reprehend ;
If you pardon, we will mend.”

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IMPETIGO CONTAGIOSA ACQUIRED IN A BACTERIOLOGICAL LABORATORY.

HENNING SCHMIDT.

Statens Seruminstitut, Copenhagen. Director : J. Ørskov, M.D.

DURING recent years, phage typing of *Staphylococcus aureus* has made it possible to demonstrate that certain strains of staphylococci most probably are connected with distinct disease entities. Staphylococci of Group I (29/52/52A/79/80) and in this group especially phage type 80, seem to be the causative organisms in several nosocomial infections, primarily furunculosis (Hess Thaysen, Riewerts Eriksen and Rosendal, 1957). Epidemics of food-poisoning have been shown to be provoked by staphylococci belonging to Group III (6/7/42E/47/53/54/70/73/75/77) and it was possible to trace the source of infection by means of phage typing of the staphylococci isolated from the stools (Gillespie, 1947; Allison, Hobbs and Martin, 1949). For many years impetigo contagiosa was regarded as a streptococcal infection; recently, however, phage typing has revealed that staphylococci belonging to Group II (3A/3B/3C/55/71) are often isolated from the impetigo sores and simultaneously from the nostrils of patients suffering from impetigo. Furthermore, experiments by Parker (1958) have shown that the staphylococci isolated from superficial infections are often egg-yolk negative (EY —).

Out of 34 strains isolated from impetigo, Spittlehouse (1955) found 31 typable strains and of these 25 (81%) were lysed by phage type 71 alone; this was the case in only 2 out of 14 typable strains isolated from sycosis barbae. In 100 cases of impetigo contagiosa, Barrow (1955) demonstrated *Staphylococcus aureus* of phage type 71 in 63 lesions and in another 26 patients staphylococci belonging to Group II were isolated from impetigo lesions. In Danish material, Schmidt, Riewerts Eriksen and Rosendal (1957) studied bacteriologically and serologically a total of 32 patients suffering from impetigo. Staphylococci were found in 31 cases and in 21 out of these, *Staphylococcus aureus* of phage type 71 occurred alone in nine cases, staphylococci of Group II + 71 were found in four cases, and finally staphylococci of Group II — 71 were demonstrated in eight cases. Thus, staphylococci of Group II were isolated in 68% of the impetigo cases.

A case of impetigo contagiosa occurring in the Phage Typing Laboratory, Statens Seruminstitut, appears to be of a certain interest, because staphylococci isolated from the lesions were probably identical with *Staphylococcus aureus* worked with in the laboratory just prior to the appearance of the impetigo lesions. Koch's postulate thus seems to be fulfilled, viz. that the

etiological agent of a disease when introduced into the body should be able to provoke symptoms and signs of the disease.

CASE REPORT.

The patient was a female laboratory technician aged eighteen, who apart from impetigo contagiosa at the age of three years had never suffered from dermatological disturbances. No cases of impetigo were known in her family when she developed an itching sore at the angle of her mouth. No special attention was paid to this, but four days later she presented with four circinate lesions of impetigo contagiosa around the mouth and a single lesion on the neck.

No haemolytic streptococci were demonstrated in the swabs and no staphylococci were isolated from her nostrils. *Staphylococcus aureus* of phage type 3A + u was isolated from her impetigo lesions and swabs from her throat showed *Staphylococcus aureus* of phage type 3B/3C/71+; however, scrutinizing the phage pattern, their identity could not be excluded and in fact these strains are considered identical both being EY— and penicillin resistant. During the week before the impetigo lesions appeared, strains were isolated in the laboratory apparently identical with the staphylococci isolated from the patient in question as far as sensitivity to four antibiotics and phage type are concerned.

The case reported here may supply further justification for the hypothesis that *Staphylococcus aureus* of Group II and perhaps especially phage type 71, may be the etiological agent of impetigo contagiosa.

My thanks are due to Kirsten Rosendal, M.D., for performing phage typing of the staphylococci isolated.

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OBITUARY.

PROFESSOR L.-M. PAUTRIER.

LUCIEN PAUTRIER was born in Provence in August 1876 and died in Strasbourg in July 1959.

He studied medicine in Paris and at an early stage in his career began to specialize in dermatology. Already in 1903 he wrote his important thesis on *Les Tuberculoses Cutanées Atypiques* and brought himself to the favourable notice of his seniors. In that year he was appointed assistant in the clinic of Brocq where he remained until 1914, eventually becoming chief assistant and *Chef de Laboratoire*. During this period he made a most important contribution to the development of systematic teaching of dermatology in the Hôpital St. Louis, his presentation of cases with histological demonstrations earning the particular praise of Darier.

At the outbreak of the Great War, Pautrier entered the army and served first as medical officer to a regiment of field artillery. In August 1914 he was awarded the *Croix de Guerre* for bravery and gallantry under fire. He was created *Chevalier* of the Legion of Honour in 1916 and eventually rose to *Grand Officier*. During the latter part of the war he was employed as a specialist in skin and venereal diseases and played an important part in the anti-venereal campaign which continued on into the post-war years.

With the end of the war, Alsace returned to France and the new French Faculty of Medicine was created at Strasbourg; Pautrier was appointed Professor of Dermatology in 1919. The clinic was built to his design and over the succeeding twenty years it was the brilliance, the personality and the inspiration of this remarkable man that made Strasbourg famous and admired throughout the dermatological world. Young dermatologists came from all over the world to study under Pautrier and received there their lifelong inspiration. Nowhere was better exemplified the value of the thorough study of comparatively few patients in contrast to the hurried sorting of hordes of cases in some larger centres. From his students and assistants he demanded careful, accurate work; in return he gave brilliant guidance, encouragement and a very genuine affection. The whole atmosphere in his clinic was a delightful combination of enthusiasm, scientific endeavour and warm-hearted friendliness. The high quality of the *Réunions Dermatologiques* and of the voluminous publications of the clinic are a permanent record of this period and a permanent contribution to knowledge.

After the outbreak of war in 1939 this happy period came to an end. The clinic moved to Clairvivre and in 1942 Pautrier was invited to Lausanne where he was professor until the end of the war. He then returned to Strasbourg but after two years he reached the age of retirement.

Pautrier was a man of tremendous energy and great brilliance; joined to this was a personality which inspired his pupils to give their best. Warm-hearted and enthusiastic, he was loved as well as esteemed. He was a man of great culture, especially fond of music and paintings.

This truly great man did not lack recognition in his lifetime. He was Honorary Doctor of four foreign universities, honorary member of thirty-four dermatological societies in various countries and had received Orders in seven foreign countries. Above all, the memory of his friendship remains with a host of his associates and former pupils all over the world.

F. R. B.



PROFESSOR L.-M. PAUTRIER.

CURRENT LITERATURE

PERCUTANEOUS ABSORPTION OF VITAMIN A. A. E. SOBEL, J. P. PARNELL, B. S. SHERMAN and D. K. BRADLEY. (1958) *J. invest. Derm.*, **30**, 315.

In rats depletion of Vitamin A becomes manifest by cessation of growth and xerophthalmia before the development of appreciable skin changes, and recovery takes place in the same order. Vitamin A though it quickly restores the area of skin to which it is being applied is not absorbed in sufficient quantity both to satisfy internal requirements and to restore the rest of the skin. Corn oil is the best vehicle from the point of view of penetration but a vaseline lanolin mixture does less harm to the skin.

Neither vitamin A nor its precursor carotene has been detected in the skin and it is not at all clear precisely how it is utilized except that it is essential to the basal layer. J. H. T. D.

URTICARIA-LIKE REACTION AFTER X-RAY TREATMENT. G. WEBER. (1958) *J. invest. Derm.*, **30**, 311.

A patient with multiple basal celled epitheliomata reacted locally to X-ray treatment with wheals. Injection of his blister serum into the skin of a normal subject rendered the site reactive in the same way to X-rays. J. H. T. D.

COMPARISON OF INHIBITORY EFFECT OF VARIOUS CHEMICAL AGENTS ON TYROSINASE ACTIVITY BY MANOMETRIC METHOD. TYO-TARO TUKAMOTO and T. TANIGUCHI. (1958) *J. invest. Derm.*, **30**, 305.

The authors describe their preparation of potato tyrosinase and the influence on its oxidation of *p*-cresol as measured by uptake of oxygen in a manometer, of some of the known tyrosinase inhibitors and a host of copper combining reagents, and compounds of sulphur and phenol, thought likely to have a similar action. J. H. T. D.

ABSORPTION OF ANTIMALARIAL DRUGS IN HUMAN SKIN. SPECTROSCOPIC AND CHEMICAL ANALYSIS IN EPIDERMIS AND CORIUM. B. SHAFFER, M. M. CAHN and E. J. LEVY. (1958) *J. invest. Derm.*, **30**, 341.

Although the mepacrine group of antimalarials have an elective affinity for epidermal protein it is impossible to demonstrate that they influence the absorption spectrum. Even if they did it would seem that the screening effect would not be appropriate to the assumed requirements. J. H. T. D.

THE EFFECT OF INTRAVENOUS FAT ON SERUM LIPIDS. M. A. EVERETT, W. D. BLOCK and A. C. CURTIS. (1958) *J. invest. Derm.*, **30**, 333.

Three normal males and 1 patient with idiopathic hyperlipaemia received intravenous infusions of 600 cc. of an emulsion of cottonseed oil. The electrophoretic pattern of the sera of the 3 normal subjects was unaltered but in the hyperlipaemic subject the elevation of serum β and α_2 globulin was substantially reduced. A year later, however, the effect was unobtainable, possibly as the result of treatment he had in the meanwhile, or possibly because of difference in the emulsion used. J. H. T. D.

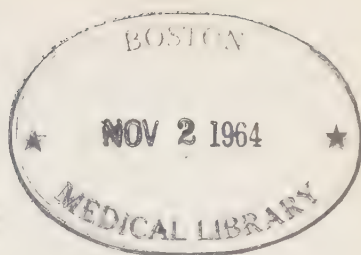
EFFECT OF ORAL STEROID ON NON-INFLAMMATORY SCALP RINGWORM. N. M. KANOF. (1958) *J. invest. Derm.*, **31**, 139.

A 9-year-old negro boy, who also had had tinea tonsurans for not more than 5 weeks, was being treated for alopecia areata with 5 mg. of metacorten 4 times a day when the ringworm disappeared, after 6 weeks of treatment. Eight other children with ringworm were then treated with the steroid and improved. Some change in the fluorescence of infected hairs was also observed.

J. H. T. D.

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